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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,733	10/01/2003	Kevin H. Gardner	UTSD:1510	4887

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
12/11/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/677,733	GARDNER ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *3, 5, and 6* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The application has been amended as requested in the communication filed November 19, 2007. Accordingly, claims 1 and 2 are canceled, and new claims 3-6 are entered.

Claims 3-6 are pending and under consideration.

New claim 3, 5, and 6 correspond to original claim 1, and claim 4 corresponds to original claim 2.

Claims 3, 5, and 6 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Fesik (WO 97/18471) in view of any one of U. S. patents 5,843,683 (Edery *et al.*); 6,291,429 (Takahaski *et al.*); 6,436,654 (Berkenstam *et al.*) for reasons of record.

In response to the Board of Patent Appeal and Interference (BPAI) decision on September 19, 2007 of affirming the examiner's rejection under 35 U. S. C. 103, applicants canceled the original claims, an presented new set of claims, and filed new arguments and a new declaration by Professor Stephen Sprang. Also, applicants stipulated the following to be true:

(i) The prior art teaches PAS domains without known cofactors and having tightly packed cores with no pre-formed ligand-binding cavities.
(ii) The prior art teaches that these PAS domains would have no NMR-apparent a priori formed ligand cavity.
(iii) That prior art teaches a variety of proteins that comprise PAS domains, and proposes functional assays for compounds which modulate their interactions.
(iv) The prior art teaches NMR analysis of receptor-ligand (enzyme-substrate) binding.

(see applicants arguments filed November 19, 2007 at page 3, paragraph 3). The focus of applicants' arguments remains that a *prima facie* case of obviousness has not been established. Applicants argue that, in the absence of a binding pocket, one of ordinary skill in the art would not have utilized NMR method to screen for ligand.

Appellants' arguments and Professor Stephen Sprang filed 11/19/07 have been fully considered, but they are found unpersuasive. The BPAI found the rejection of record appropriate and a *prima facie* case of obviousness has been established. The questions raised by the BPAI, which necessitated the new rejection by the BPAI, is now answered by the appellants. The appellant has not challenged the examiner position that the proteins of the prior art meet all the limitation of the claims, and that the prior art provides motivation and an assay to identify modulators. The NMR method taught by Feisk is one of the most sensitive methods that detect the interactions between a protein and a small molecule. Even the binding of molecules that binds weakly to a target protein can be detected effectively by NMR due to the sensitivity of an NMR signals to the local environment of each atom. Other advantages include easy to use,

well developed and reliable technology, and amenable to automation. Thus, if a motivated one of ordinary skill in the art expecting to find a modulator of the PAS domain activity, he/she would also be motivated to use the most sensitive method of detecting the interaction, i.e., NMR.

As indicated in the Examiner's answer mailed January 24, 2007, the NMR method taught by Fesik is a general method of identifying small molecules that bind to proteins and it does not require any knowledge of the structure of the target protein. See page 5, second paragraph, of the Examiner's answer. Item 3 of Professor Sprang's declaration under 37 CFR 1.132 is particularly troubling to this examiner. On one hand applicants stipulate that the prior art teach the proteins used in the method, provide motivation to identify modulator of the PAS domain, and functional assay to identify said modulator. On the other hand, Professor Sprang exclude one of the most sensitive methods for identifying small molecules that interacts with proteins. If a small molecule binds to PAS domain, one of ordinary skill in the art would expect to observe the effects of binding the small molecule on the NMR signals of the PAS domain. Neither the applicants nor Professor Sprang offer any explanation for this contradiction.

The fact that the NMR method cannot observe certain signals in the absence of a ligand does not mean that the ligand-binding site is not formed or is formed incompetently. The major advantage of the NMR method over any other screening method is that it observes the binding of the small molecule directly to the target protein in its native environment, i.e., in aqueous solution. Unlike crystals, protein molecules are neither static nor stationary in solution. Various protein molecules are constantly sampling different conformations and orientation relative to the magnetic field, i.e., tumbling in the magnetic field. If the changes are fast on the NMR experimental time scale, an average signal will appear for all the conformers and positions of the molecule relative to the magnetic field. If, however, the conformation changes are slow relative to the time scale, the NMR signals of some residues become much broader or not observable at all in many cases. There is no reason to believe that most abundant conformation in solution which is observed by NMR is the most relevant conformation for binding a small molecule or a large biological target molecule. Thus, one of ordinary skill in the art would not have been discouraged from using the Feisk's method because the presence or absence of some NMR peaks indicating the absence or presence of a ligand-binding site. The ordinary skill in the art would have known of the presence of the ligand-binding cavity because the protein has an activity in solution. There is no reason for one of ordinary skill in the art to carry out the monumental task of fully assigning all the ^{1}H, ^{13}C and ^{15}N NMR signals of a PAS domain to carry out the Feisk's for a PAS domain. The NMR signal due to residues involved in the interaction between the PAS domain and a foreign or native ligand can be identified in the presence of a chemical compound even those that weakly interact with the protein with relative ease by comparing the spectra in the presence and absence of the ligand. See Whitty *et al.* at page 114, middle column, starting at line 16 from the bottom. Appellants

should note that references 14-16 are all published before the earliest priority date for the instant application and represent the state of the art at the time of invention. NMR signals for ^{1}H, ^{13}C and ^{15}N from amino acid residue in the binding cavity are perturbed the most in the presence of a ligand, and thus, can be identified and assigned with relative ease. The binding of the ligand to the PAS domain would be expected to favor the conformation comprising the binding cavity.

Also Professor Sprang alleges that the PAS domains are involved in protein/protein interaction making them members of a class of targets that are widely considered "undruggable", and quotes Whitty *et al.* to support his statement. Whitty *et al.* is a general review article which discuss inhibition of protein/protein interaction. The article takes the view that developing modulator protein activity involving protein/protein interaction is difficult, but not impossible. Figure 1 shows several chemical structures involve of modulating specific protein/protein interaction. Structure (a) of Figure 1 was reported by cited reference 32, Tiliey *et al.* (1997) published well before the earliest priority date for the instant application. Thus, providing expectation of success to one of ordinary skill in the art that modulators of protein/protein interaction are possible to identify. Thus, neither of the argument provided by the appellants nor the declaration of Professor Sprang overcome the obviousness rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nashed/
Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656